Jpn. J. Med. Mycol.
Vol. 42, 75 - 80, 2001
ISSN 0916-4804

Review

US-Japan Workshops in Medical Mycology: Past, Present and Future

Dennis M. Dixon, Ph.D.

Chief
Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland USA 23298

Abstract

The Extramural Mycology Program of the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) has organized and implemented a five workshop series in medical mycology during a critical period in the evolution of contemporary medical mycology (1993 to 2000; http://www.niaid.nih.gov/dmid/fungal/#2e). The goals of the workshop series were to- initiate interactions; build collaborations; identify research needs; turn needs into opportunities; stimulate molecular research in medical mycology; and summarize recommendations emerging from the workshop proceedings. A recurring recommendation in the series was to foster communications within and beyond the field of medical mycology. US-Japan interactions were noted as one specific example of potential information exchange for mutual benefit. The first formal action directed at this recommendation was the workshop "Emergence and Recognition of Fungal Diseases" convened under the auspices of the US-Japan Cooperative Medical Science Program (USJCMSP; http://www.niaid. nih.gov/dmid/us%5Fjapan/default.htm) in Bethesda, Maryland USA on 30 June 1999 (D.M. Dixon & T. Matsumoto, co-chairs). A major goal of the workshop was to present contemporary medical mycology to the joint Committee of the USJCMSP through representative research presentations in order to make the Committee aware of current status in the field, and the potential for scientific interactions. The second formal action is the workshop, under the auspices of the Japanese Society for Medical Mycology "Medical Perspectives of Fungal Genome Studies" scheduled for 28 November 2000 in Tokyo, Japan (T. Matsumoto & D.M. Dixon, co-chairs). The NIAID Mycology Workshop series recommended interactions between the following groups: academic and pharmaceutical; medical and molecular (model systems); medical and plant pathogens; basic and clinical; mycologists and immunologists. The first two US-Japan workshops can be viewed as consistent with these recommendations, and serve as a Western/Fastern gateway for exchange. The focus of the second US-Japan workshop on genorne projects for the medically important fungi provides an excellent model for international communications. Given the tsunami of information that is flowing from genomics and bioinformatics, it is clear that global interactions will be essential in managing and interpreting the data.

Key words: Mycology, NIH, fungus, genome, vaccine, international, communication

Introduction

Medical mycology has enjoyed a rich history in the United States. The endemic mycoses, especially blastomycosis, coccidioidomycosis and histoplasmosis, have afforded ample opportunities for studies of direct relevance to human health. The United States is either the principal country of presentation (blastomycosis and histoplasmosis) or a significant country of presentation (cocci- dioidomycosis) for these life-threatening infectious diseases. The opportunistic mycoses, especially aspergillosis and candidiasis, are increasingly prevalent in the United States because of the rapidly growing numbers of persons at risk for infection derived from advances in modern medicine that result in the disturbance of normal flora or normal host defenses.

Medical mycology at the National Institutes of Health (NIH) in the United States can be summarized as follows. The NIH is a component of the Department of Health and Human Services (DHHS) in the Executive Branch of the United States Government. The organizational structure of the NIH can be gathered from the website, http://www.nih.gov/. The primary organizational units are Institutes and Centers. Representative Institutes that focus on medical mycology include: The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Dental and Craniofacial Research (NIDCR), the National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI). Research is addressed by the NIH in either of two general ways: Intramural Programs that are conducted at the NIH in laboratory and clinical studies by NIH staff, and Extramural Programs that are administered through grants and contracts to grantee eligible institutions such as universities in the United States (and through- out the world). The NIAID is the lead Institute for medical mycology. Both Intramural and Extramural programs exist and are robust. Extramural programs are represented in both the Division of Microbiology and Infectious Diseases (DMID) and in the Division of AIDS (DAIDS). The majority of the awards are based in the Bacteriology and Mycology Branch, DMID.

The NIAID launched a five part series in medical mycology beginning in 1993 (Table 1). The series was developed and implemented in collaboration with community input and support. Five topic areas were chosen and were 1) Molecular Medical Mycology; 2) Diagnosis and Treatment of Systemic Mycoses; 3) Immunology --- Antigenic Peptides, Glycobiology, and Vaccines;

Table 1. The National Institute of Allergy and Infectious Diseases (NIAID) Medical Mycology Workshop Series[1]

	Topic	Year
1.	Molecular Medical Mycology	1993
2.	Diagnosis and Treatment	1994
3.	Immunology I (Protective Antigens)	1995
4.	Immunology II (Host-Pathogen Interactions)	1997
5.	Epidemiology	2000

[1] The full title for each workshop and a summary can be accessed from the NIH Home Page (www.nih.gov) by selecting the NIAID home page from the Institutes and Centers menu, then using the search engine and typing mycology workshop. The current posting site is: http://www.niaid.nih.gov/dmid/meetings/.

Table 2. Summary List of Ten Key Accomplishments from the NIAID Medical Mycology Workshop Series

1. Woods Hole Course in Medical Mycology[1]
2. Fungal Genome Projects
3. Development of Genetic Systems
4. Cryptococcal Monoclonal Antibody (MAb 18B7) Clinical Treatment Project[2]
5. Cryptococcal Working Group[3]; other newsgroups
6. US-Japan Workshops
7. Requests for Applications[4] (RFAs; targets grants)
8. Requests for Proposals[4] (RFPs; targets contracts)
9. Program Announcements[4] (PAs; grants)
10. The Intangibles

[1] Internet site is http://hermes.mbl.edu/ and search for mycology, or summer courses.

[2] The Cryptococcal monoclonal antibody project referenced in this table and report is 18B7 and was initiated by Dr. Arturo Casadevall and moved sequentially through scale up manufacturing and Phase I clinical testing. For a description of the foundational science, refer to the Internet CRISP site (http://commons.cit.nih.gov/crisp/CRISP.Generate_Ticket) and search for 18B7.

[3] (http://www.acs.ucalgary.ca/~cmody/)

[4] Internet accessed, text based search by key word will reveal current and archived solicitations of interest. (http://grants.nih.gov/grants/guide/index.html)

Woods Hole Course in Molecular Medical Mycology

(http://hermes.mbl.edu/education/courses/special_topics/momy.html)

The first workshop in the series noted the need for an ongoing forum for interactions in

contemporary medical mycology in a training setting that blended the technology from the non-medical model fungi with the needs of the medically important fungi. Participants from the first workshop continued to develop the concept, and were given start up funding by the Burroughs Wellcome Fund to establish the Woods Hole Course in Molecular Medical Mycology. Drs. John E. Edwards, Jr., Paul T. Magee and Aaron Mitchell developed and launched the course in 1997, and have continued to serve as Co-directors in residence during the three-week course.

Genome Projects

The normal mechanism for investigator initiated research applications at the NIH is the ROI grant that has two operational features of direct relevance to the advance of genome sequencing projects: (1) the cost is limited to $500,000 before overhead; and (2) peer review. The cost limitations are obvious. It would be difficult to sequence the complete genome of a fungus over the average three-year project funding period for this amount.

The limitations of the peer review system are less obvious, but relate to the ability of technology driven projects to compete successfully with hypothesis driven, exploratory research. Nonetheless, there are now three medically important fungi that are the subject of NIH- funded, whole genome sequencing projects conducted under the ROI mechanism: Candida *albicans, Cryptococcus* neoformans, and *Pneumocystis* carinii. All three projects are characterized by co- funding from multiple sources and international collaborations, including Japanese representation. A major opportunity occurred recently when the NIAID announced a new process for pathogen genome sequencing (http://www.niaid.nih.gov/dmid/genomes/default.htm). Two significant features of the process are: (1) total costs of $1.5 M are allowed for each of two years; and (2) a select list of targeted organisms is eligible for the new process. Two fungi are represented on the first list of five targeted organisms: Aspergillusfumigatus *and Cryptococcus neoformans* (to complement the existing, smaller projects). The priority list posted for FY 2001 includes two additional fungi: *Coccidioides immitis and Histoplasma capsulatum* (http://www.niaid.nih.gov/dmid/genomes/priorities.htm).

Moving Basic Research Discoveries on to Clinical Implementation

The third workshop, with an emphasis on fungal vaccines, provided ample opportunity for interactive discussion. The concept of functional antigens was advanced, where clinically useful antigens were appreciated as those generating a protective immune response. Fungal vaccine research provides an excellent model of interdisciplinary approaches contributing to a common goal. Research on fungal vaccines should involve research collaboration among the following: molecular biology; organism-specific biology; biochemistry; immunology; animal model development; genomics; and bioinformatics. Such interactions hold great potential to stimulate and strengthen the central discipline of medical mycology and ultimately could contribute a useful means of prevention. Additionally, there could be results of importance to the related needs of diagnosis and treatment. One specific recommendation was to explore the possibility of US-Japan interaction in the above endeavors where there could be mutual reinforcement. Thus, a specific accomplishment attributed to this workshop series could be the US-Japan Cooperative Medical Science Program Workshop in Medical Mycology, held in Bethesda, MD USA, and its evolution to a second, independent theme-based workshop in Tokyo on fungal vaccines.

Additional results attributed to the third NIAID mycology workshops are: the Cryptococcal Working Group (CWG) and the NIH funded clinical trial of cryptococcal monoclonal antibody Mab 18.B7. The CWG formed at the workshop (http://www.acs.ucalgary.ca/~cmody/) and developed an organized structure for ongoing communications. The Cryptococcal monoclonal antibody project, an NIAID sponsored, Phase I clinical trial, A Phase I Evaluation of the Safety and Pharmacodynamic Activity of a Murine Derived Anticryptococcal Antibody 18B7 in HIV-Infected Subjects Who have Responded to Therapy for Cryptococcal Meningitis, can be viewed as addressing the need to take basic research findings and move them forward to clinical testing and as a means to explore functional antigens that may be immunologically protective.

For completeness, the remaining items on the representative list of ten are: RFAs (Requests for Applications); RFPs (Requests for Proposals); and PAs (Program Announcements); and

"intangibles." The first three are administrative means that the NIH uses to advertise (solicit) specific needs and interests. Specific examples of all three (RFAS, RFPS, and PAs) can be found for current and archived solicitations in the NIH Guide for Grants and Contracts (http://grants1.nih.gov/grants/guide/index.html). Mycology related solicitations can be identified by using the text search feature and mycology as the key word. The "intangibles" are those general benefits that derive from having developed a sense of community and progress in specific areas of the field of medical mycology.

The First US-Japan Workshop in Medical Mycology

The Subcommittee of the US-Japan Cooperative Medical Science Program (USJCMSP) at its winter meeting in Hawaii, 1998 approved a workshop on medical mycology for presentation to the joint Committee at its 30 June 1999 meeting in Bethesda, Maryland USA. The purpose of the workshop was to present representative topics in medical mycology to members of the joint Committee to place the field in proper context, and, in the spirit of the USJCMSP, to provide a forum and points of contact for any future cooperation or interaction. The first workshop, "Emergence and Recognition of Fungal Diseases" was therefore convened under the auspices of the US-Japan Cooperative Medical Science Program. The workshop was chaired by Drs. Dennis Dixon and Tadahiko Matsumoto and featured four speakers from the United States and three from Japan (Table 3). Representative topics in medical mycology were chosen for presentation, as well as a general clinical overview and general perspectives from basic research. The clinical overview presentation clearly documented the rise of invasive mycoses into prominence due risks related to cancer chemotherapy, bone marrow or stem cell transplantation, organ transplantation, low birth weight, AIDS, diabetes mellitus, inherited immunodeficiencies, medical intensive care procedures, or complicated surgery.

The complexity in scope was demonstrated for the range of different fungal pathogens (yeasts, moulds, and dimorphic fungi), their pathogenic mechanisms, and the disease presentations (allergic; invasive, or opportunistic). Representative examples were given of individual dematiaceous fungi that can cause a spectrum of disease presentations ranging from dermatological to disseminated infection with central nervous system involvement. It was clear that substantial advances have occurred in recent years on some of the cellular bases of the host vulnerability, and the pathogenic mechanisms of the fungi. Further, it was clear that the basic research advances in medical mycology are indeed advancing to clinical testing as evidenced by a presentation on passive immunotherapy as a potential adjunct to antifungal treatment of cryptococcal meningitis.

The Second US-Japan Workshop in Medical Mycology: Medical Perspectives of Fungal Genome Studies

The first workshop was authorized by the Subcommittee of the USJCMSP as a one time event for the purposes described above. The USJCMSP was chosen for the first workshop because it was the most obvious means by which to effect the kinds of interactions suggested at the NIAID mycology workshops. However, to build on the experiences of the first workshop,

Table 3. The First US-Japan Workshop in Medical Mycology: Emergence and Recognition of Fungal Diseases[1]

Topic	Speaker	Country
Introduction	Dr. Dixon	USA
Clinical Overview	Dr. Walsh	USA
Melanized Fungi	Dr. Matsumoto	Japan
T-cell Receptor Usage	Dr. Deepe	USA
Hypersensitivity	Dr. Ando	Japan
Passive Immunization	Dr. Casadevall	USA
Virulence Factors	Dr. Nozawa	Japan
Perspectives	Dr. Kwon-Chung	USA
Closing and Discussion	Drs. Dixon & Matsumoto	USA

[1] Conducted under the auspices of the US-Japan Cooperative Medical Science Program (USJCMSP) as a one time workshop to present representative topics in medical mycology to members of the Joint Committee to place the field in proper context, and, in the spirit of the USJCMSP, to provide a forum and points of contact for any future cooperation or interaction. The workshop was held 30 June 1999 meeting in Bethesda, Maryland USA, and was co-chaired by Drs. Dennis M. Dixon and Tadahiko Matsumoto.

Table 4. The Second US-Japan Workshop in Medical Mycology: Medical Perspectives of Fungal Genome Studies[1]

Topic	Speaker	Country
Introduction	Dr. Matsumoto	Japan
Genome Studies in Medical Mycology	Dr. Makimura	Japan
Cryptococcus	Dr. Nierman	US
Candida	Dr. Iwaguchi	Japan
	Dr. Magee	US
Aspergillus	Dr. Machida	Japan
	Dr. Denning	UK
Pneumocystis	Dr. Nakamura	Japan
	Dr. Smulian	US
Conclusion & Closing Remarks	Dr. Dixon	US
Closing Address	Dr. Nozawa	Japan

[1] The second U.S. Japan workshop in medical mycology was conducted under the auspices of the Japanese Society for Medical Mycology. It was held on 28 November 2000 in Tokyo, Japan and was chaired by Drs. Tadahiko Matsumoto and Dennis M. Dixon. Sponsorship was also provided by the Burroughs Wellcome Fund and the National Institutes of Health.

and to complete the cycle of the conventional US- Japan sequence that involves alternating meeting sites between the US and Japan, a second workshop was planned independent of the formal USJCMSP structure. The Second US-Japan Workshop in Medical Mycology: Medical Perspectives of Fungal Genome Studies, was conducted under the auspices of the Japanese Society for Medical Mycology. It was held on 28 November 2000 in Tokyo, Japan and was chaired by Drs. Tadahiko Matsumoto and Dennis M. Dixon (Table 4). Sponsorship was also provided by the Burroughs Wellcome Fund and the National Institutes of Health.

Another key distinction of the second workshop was the decision to focus on a single topic of keen importance to the field. Genome projects and genomics, the focus of the second US-Japan workshop, is clearly of central importance not only to medical mycology, but also to all of biology. All four of the genome projects on the program were noted to involve international collaborations with both US and Japanese representation.

The Aspergillus fumigatus genome project is an excellent example of both the importance of genome studies to advancing a field, and the opportunity for international interactions. The field of contemporary science for *A. fumigatus* has lagged behind both public health need and the scientific progress of other medically important fungi. It has been difficult to stimulate the accumulation of knowledge on pathogenesis as well as molecular mycology for the A*spergillus* species of importance to humans. For evidence of this in the large, competitive funding area of the NIH, conduct a simple NIH CRISP computer search to compare funded research efforts on *Aspergillus* versus Candida (http://crisp.cit.nih.gov/). The eligibility of *A. fumigatus* for the new NIH process addressing pathogen genome sequencing could come to represent a hallmark event in medical mycology. A research application competed favorably and an award was recently made to Victoria University of Manchester, UK to begin the whole genome sequencing of this (large genome - 30 Megabase) fungus. The project is particularly instructive for addressing large projects where no one single funding source is sufficient to complete the entire project in a rapid timeline.

The background is as follows: Dr. David Denning, the principal investigator of the project, realized the need to involve an international community of medical mycologists and specialists in genome sequencing to develop a critical mass of investigators, and to recognize discipline specific expertise. An international team was assembled to collaborate on the whole genome sequencing coordinated through the University of Manchester. A BAC library was developed through a grant from the Wellcome Trust to University of Manchester to serve as a pilot project and provide a logical means to manage the project in modules based on BAC allocation as funding sources were identified to allow the data to unfold in increments that were individually and collectively useful. An alternative approach under consideration is the allocation of portions of the whole genome by apportionment of chromosomal bands from CHEF gels. The Burroughs Wellcome Fund provided a pilot project grant to Dr. Joan Bennett in the USA who facilitated the integration of the US investigators into the project. The NIH grant to enable 30% of the genome to be sequenced represents a cornerstone in the project. The Sanger Center with funding through the Wellcome Trust has played an equally key role in generating preliminary feasibility projects, and in continuing to offer competitive opportunities that can complement the ongoing project. Also, the Burroughs Wellcome Fund was a vital partner in facilitating the communications amongst US investigators (e.g., The Institute for Genome Research - TIGR is the sequencing center for the NIH grant), and to maximize efficiency as a consequence. Therefore, the project exemplifies the need to communicate across geographic and funding barriers. In summary, the *A. fumigatus* genome project could serve as a model for international medical mycological research of the future.

The field of medical mycology is in a position to draw upon a base of six major sequencing projects in a forward thinking and collective way *(Saccharomyces cerevisiae and Neurospora crassa as* models for yeasts and moulds, and *A. fumigatus, C. albicans, C. neoformans, and Pneumocystis carinii* as model pathogens). The nascent field of comparative genomics provides fertile ground for collaborative venture. The magnitude of information that is resident in these projects is formidable. Several models have been proposed for managing bioinformatics approaches to the genomes of microbes). One is to have a single repository serve as the focal point for gathering and posting the accumulated body of information stemming from the genome tide. A second, is the individual investigator approach to curating the information

independently, and contributing the information to the literature or the Internet. Either could work, and has been discussed. Either approach offers the opportunity for international cooperation amongst mycologists and computational biologists. It is perhaps in such an opportunity that the compelling medical need for better understanding of the medically important fungi can serve to catalyze the international mycological efforts. International meetings were key in establishing the dynamic team approach to *the Aspergillus and Pneumocystis* genome projects, and are likely to be key to future success. The meetings were focused on the science, and the various attendees had defined roles and responsibilities.

Summary

During the course of the five workshops in the NIAID series in medical mycology (Table 1), the following areas for enhancing bi-directional communication were noted: academia and pharmaceutical; medical and molecular (model systems); medical and plant pathogens; basic and clinical mycology; and medical mycologists and immunologists. Communications between and among these groups currently occur at the international level, but could be enhanced. The first two US- Japan workshops provide an example of bilateral communication between two hemispheres that could benefit from enhanced communications. The fact that each of the four medically important genome projects discussed at the second workshop contains examples of Eastern-Western collaborations is instructive for two reasons: first, that the interactions occurred as a consequence of the scientific need and opportunity; and second, that for the *Aspergillus and Pneumocystis* genome projects, the pivotal international meetings were focused on specific scientific goals relating to an individual project. Therefore, regardless of the future of mycology meetings dedicated to the topic of US and Japanese interactions in mycology, the first two such workshops have served to advertise that such interactions are important and could even serve to stimulate additional individual interactions. Given the growing number of regularly scheduled annual meetings in the sciences, there is some logic to letting the meeting structure derive from scientific need, and be a component of individual scientific projects, rather than a consequence of the completed scientific efforts.

Reference

1. Fraser CM, Eisen JA, Salzberg SL: Microbial genome sequencing. Nature **17;** 406(6797): 799- 803, 2000.